Use of Anticholinergic Drugs and its Relationship With Psychological Well-Being and Mortality in Long-Term Care Facilities in Helsinki

Aalto, Ulla Liisa

2018-06

Aalto , U L , Roitto , H-M , Finne-Soveri , H , Kautiainen , H & Pitkälä , K 2018 , ' Use of Anticholinergic Drugs and its Relationship With Psychological Well-Being and Mortality in Long-Term Care Facilities in Helsinki ' , Journal of the American Medical Directors Association , vol. 19 , no. 6 , pp. 511-515 . https://doi.org/10.1016/j.jamda.2017.11.013

http://hdl.handle.net/10138/301998
https://doi.org/10.1016/j.jamda.2017.11.013

Use of anticholinergic drugs and its relationship with psychological well-being and mortality in long-term care facilities in Helsinki

Aalto UL MD[1,2], Roitto HM MD[3], Finne-Soveri UH MD, PhD[1,4], Kautiainen H[5], Pitkala KH MD, PhD[2,5]

[1] Department of Social Services and Health Care, Home-care services, City of Helsinki, Finland

[2] University of Helsinki, Department of General Practice, Helsinki, Finland

[3] Department of Social Services and Health Care, Geriatric Clinic, City of Helsinki, Finland

[4] National Institute for Health and Welfare, Helsinki, Finland

[5] Helsinki University Hospital, Unit of Primary Health Care, Helsinki, Finland

Correspondence to:

Ulla L. Aalto

Address: PO BOX 6540, FI-00099 Helsinki city, Finland

Phone: +358503535030

Email: ulla.aalto@fimnet.fi

Abstract

Objectives: 1) To assess the burden of drugs with anticholinergic properties (DAPs) and associated factors in long-term care facilities, and 2) to explore how psychological well-being and mortality are associated with the use of DAPs.

Design: Cross-sectional study and one-year follow-up of all-cause mortality.

Setting and Participants: All 4449 older people (>65 years) living in nursing homes and assisted living facilities in Helsinki in 2011 were recruited. After refusals and excluding residents with severe dementia, 2432 participants remained.

Measurements: Data on demographics, drug use, and medical history were collected by trained nurses using a structured assessment. Psychological well-being (PWB) of participants was assessed by six questions. resulting in a validated PWB score (range 0-1). Mortality data were retrieved from central registers. The total number of anticholinergic drugs was determined according to the Anticholinergic Risk Scale.

Results: Of participants, 51% used at least one DAP. DAP users were younger and had better cognition than nonusers. There was a linear relationship between the number of DAPs used and poorer PWB. A similar trend was present between the number of DAPs and poorer PWB both among those with and without depression and among those with and without functional dependency. No difference in mortality existed between DAP users and nonusers.

Conclusion: Despite DAP users being younger and having better cognition, they had poorer PWB. Clinicians should carefully consider the potential benefits and harms when prescribing DAPs to older people

Keywords: anticholinergic drug, aged, psychological well-being, mortality

Introduction

Polypharmacy is common among older adults in nursing homes.[1] Nursing home residents have a high number of comorbidities that need to be appropriately managed. The treatment must alleviate symptoms and provide sufficient palliative care to achieve good quality of life (QOL). Drugs with anticholinergic properties (DAPs) are mainly considered inappropriate medications for older persons, and thus, to be avoided.[2,3] However, they are used for a large number of conditions, mainly to manage symptoms.[4] The prevalence of anticholinergic drug use in nursing home populations varies between 10.5% and 77% depending on the various definitions and scales used for DAPs as well as the different populations.[5,6,7]

Anticholinergic drugs are considered to be potentially harmful because of adverse effects on both the peripheral and central nervous systems.[8] Adverse effects include, for example constipation, dryness of mouth, dry eyes, and tachycardia[3] as well as dizziness, potentially leading to falls.[9] Frail older people are particularly vulnerable to central adverse effects such as dizziness, sedation, and cognitive decline.[10] Numerous studies have explored whether the burden of using several DAPs leads to worse outcomes than more moderate use of DAPs.[11] The cognitive side effects seem to be more significant with a higher burden of DAPs irrespective of the DAP scale used.[11] Studies exploring the association of DAPs with mortality have shown controversial findings.[9] To our knowledge, only a few studies have examined the relationship between the use of DAPs and QOL. While one study found an association between use of DAPs and psychological well-being (PWB),[12] another found no such association.[13]

The objective of this study was to investigate the use of DAPs among residents in long-term care facilities and associated factors, particularly PWB and mortality. We especially wanted to clarify the relationships between a higher number of DAPs and participants´ characteristics, PWB, and mortality.

Methods

The current study is part of a larger study[14,15] investigating older people´s (>65 years) nutritional status and associated factors in all long-term care facilities. In 2011, cross-sectional data were collected for all older persons living in institutional care, both assisted living facilities and nursing homes in Helsinki (n=4449). Assisted living facilities are similar to traditional nursing homes with respect to providing 24-hour nursing care, but have a more home-like environment. Assisted living facilities include also group homes for patients with dementia. Of participants, 1097 were excluded because of dementia and not having a close proxy to give informed consent or patient refusal. In addition, we excluded residents with severe dementia (CDR 3) to include only those able to respond to PWB. So, finally, 2432 participants remained. Informed consent was obtained from each participant and in case of significant cognitive decline (CDR 2) from their closest proxy. This study was approved by the Helsinki University Central Hospital Ethics Committee.

In each unit, a trained nurse assessed the resident's status by retrieving background data from medical records on demographic factors, active diagnoses (chronic conditions and acute illnesses) and medication, and carried out the assessments and interviews according to a structured questionnaire. Each resident was assessed over the course of one day, and all data concerning medication use was a point prevalence on the same day.

Nutritional status was assessed by the Mini Nutritional Assessment (MNA).[16] MNA includes questions concerning nutritional status and general health status. A total score less than 17 points indicates malnutrition, 17-23.5 points a risk for malnutrition, and over 23.5 points normal nutritional status, with the maximum score being 30 points. Cognitive function was evaluated by Clinical Dementia Rating (CDR) scale "memory" item (0-0.5, no or possible memory problems; 1, mild problems; 2-3, moderate or severe problems), which is a validated method to assess the stage of dementia.[17] Resident´s ability to move was assessed by the question "Is the resident able to move inside?" (1= yes, 2= no, needs a stick or a walker, 3= no, needs another person´s aid, 4= no, can´t walk at all). Those in groups 1 and 2 were considered to move independently. Dependence in

activities of daily living (ADL) was assessed by a 4-point scale according to CDR "personal care" item (1= totally independent; 2=needs prompting, 3=requires assistance in dressing, personal hygiene, and keeping of personal belongings, 4=requires much help with personal care; often incontinent).[17] Those in groups 3 and 4 were considered to be dependent on help from other people. All active diagnoses retrieved from medical records were taken into account when constructing the Charlson Comorbidity Index (CCI), which is a method to evaluate the number and severity of comorbid conditions.[18]

The use of medications was retrieved from medical records during the assessment day. Residents were considered to be a regular drug user if their medical charts indicated a regular sequence for its dosage. All drugs were classified according to the Anatomical Therapeutic Chemical Classification System (ATC) (WHO Collaborating Centre for Drug Statistics Methodology).[19] All DAPs used by the participants were listed and classified according to the Anticholinergic Risk Scale (ARS), which is a list of commonly prescribed medications with anticholinergic potential.[3] We calculated the total number of DAPs used, and the participants were divided into four groups based on usage: Group 0 (using no DAPs) (n=1191), Group 1 (using one DAP) (n=682), Group 2 (using two DAPs) (n=313), and Group 3 (using three or more DAPs) (n=246). Some typical symptoms in older people, such as dry mouth and constipation, were also assessed for they are known to be common peripheral side-effects of DAPs.[20]

PWB was evaluated by asking the residents the following six questions: 1. "Are you satisfied with your life? (yes/no); 2. "Do you have zest for life?" (yes/no); 3. "Do you feel needed?" (yes/no); 4. "Do you have plans for the future?" (yes/no); 5. "Do you suffer from loneliness?" (seldom or never/sometimes/often or always); 6. "Do you feel depressed?" (seldom or never/sometimes/often or always). The PWB score was created from these questions and counted as follows: 0 points ("no" in questions 1-4, "often or always" in questions 5-6), 0.5 point ("sometimes" in questions 5-6), and 1 point ("yes" in questions 1-4, "never or seldom" in questions 5-6), and the total number of

points was then divided by the number of questions answered. Thus, the range of PWB scale is from 0 to 1. These questions have been used since 1989 in several studies[21,22,23] and their validity is established. Each question shows good reliability,[22] significant prognostic validity,[21] and good concurrent validity with WHOQOL-Bref.[24] Residents´ subjective health (self-rated health, SRH) was evaluated with the question "How do you rate your current health status?" (1 = healthy, 2 = quite healthy, 3 = unhealthy, and 4 = very unhealthy). Those answering "healthy" and "quite healthy" were considered as having good self-rated health.

Mortality was retrieved from central registers over a one-year follow-up.

Statistical significance for the hypothesis of linearity across categories of anticholinergic properties groups were evaluated using generalized linear models (e.g. analysis of variance and logistic models) with appropriate distribution and link function. Models included age and gender as covariates. In the case of violation of assumptions (e.g. non-normality), a bootstrap-type method was used (10 000 replications) to estimate standard error. The normality of variables was evaluated by the Shapiro-Wilk W test. All analyses were performed using STATA 15.0.

Results

A total of 1241 patients (51%) were DAP users (groups G1-3) and 1191 patients (49%) were not using any DAPs (group G0). The DAP users were significantly younger than the nonusers (p for trend <0.001). Those using multiple DAPs were less often widowed. The nonusers had more often moderate cognitive impairment graded by CDR memory scale (35%) than the DAP users. The corresponding figures in G1, G2, and G3 were 33%, 29%, and 24%, respectively (p for trend 0.007). No significant differences existed between groups with respect to gender distributions, education, nutritional state, or dependency in ADL personal care or ability to walk inside (Table 1).

The groups differed from each other in self-rated health. In G3 only 53% of participants considered their subjective health as good. For G0, G1, and G2, the figures were 66%, 65%, and 68%,

respectively (p for trend 0.016). Those not using DAPs had a significantly higher CCI (2.4) than those using DAPs (p for trend 0.006). Of nonusers, 64% suffered from dementia, whereas in DAP users dementia was slightly more common in G1 (68%) and prevalence of dementia decreased in G2 (63%) and G3 (46%) (p for trend 0.011). DAP users suffered more often than nonusers from depression, other psychiatric disorders, and Parkinson´s disease.

There was a stepwise increase in the mean number of regularly used drugs from G0 to G3 (p for trend <0.001), and the same pattern was seen in the mean number of drugs used *pro re nata*. The groups did not differ in suffering from dry mouth or constipation. The nonusers had significantly better PWB (0.73 ±0.24) than those using DAPs, and the PWB score had a decreasing trend from G0 to G3. The figures for G1, G2, and G3 were 0.67 ±0.26, 0.67 ±0.25, and 0.62 ±0.28, respectively (p for trend < 0.001, adjusted for age and gender) (Table 2).

When the DAP user groups were stratified according to diagnosis of depression, both groups showed a similar decreasing trend in PWB with increasing use of DAPs (p for linearity in DAP groups <0.001, p for depression <0.001, p for interaction =0.16; adjusted for age and gender). Similarly, when the DAP user groups were stratified according to dependence in ADL (CDR personal care 0-1 vs. 2-3), both groups showed a decreasing trend in PWB with increasing use of DAPs (p for linearity in DAP groups <0.001, p for dependency=0.44, p for interaction =0.14; adjusted for age and gender) (Figure 1).

No significant difference emerged between groups in all-cause mortality at the one-year follow-up (p for trend 0.11, adjusted for age and gender) (Table 2).

Discussion

Our study suggests that DAPs are administered to younger and more robust residents. Despite their younger age, better nutritional status, and better cognition and functioning, the PWB of DAP users was lower than that of nonusers. Furthermore, the more DAPs used, the poorer the PWB appeared

to be. In addition, a similar linear trend of DAPs on PWB was seen both among those with and without depression and among those with and without functional dependency.

Strengths of this study include the relatively large sample size. Trained nurses collected clinical data, and information on medical diagnoses and medications used was retrieved from medical records, resulting in high validity of data. Mortality data were retrieved from central registers; in Finland with identity codes, it is known to be 100% complete. The sample is well representative of the older, frail people living in institutional care suffering from a wide range of comorbidities and polypharmacy and having moderate problems with cognition. The PWB scale is a well-validated tool used in many earlier studies.

Several limitations of the study must also be noted. One is its cross-sectional nature, which does not allow definite conclusions to be drawn on causal relationships between the use of DAPs and PWB or mortality. Possibly some underlying conditions or diseases, e.g. depression, might explain the poorer PWB among those using more DAPs. To examine this possibility, we conducted further analyses that explored the relationship between use of DAPs and PWB separately among those with and without depression, and found no interaction in this respect. Thus, it is unlikely that there was confounding by indication among those with depression which would explain the poor PWB.

An important point of discussion is that no international consensus exists regarding which of the many anticholinergic drug lists should be used. We chose the ARS[3] to categorize the medications because it has been fairly widely used and it allows also international comparison. However, all of the medications listed in ARS are not used or even available in Finland (benztropine, chlorpheniramine maleate, cyproheptadine, thiothixene, cyclobenzaprine, desipramine, and methocarbamol). On the other hand, the ARS might underestimate anticholinergic drug use since it does not include some drugs considered to have anticholinergic properties such as doxepine.[2] In addition to the above-mentioned limitations, only the numbers of anticholinergic drugs were calculated, not the total anticholinergic burden as described in ARS.

The prevalence of DAP use in these long-term care facilities was 51%, which is fairly consistent with earlier findings in studies using ARS in similar populations.[25,26] However, studies using other definitions for DAPs show differing prevalences.[5,7,27,28] In line with previous studies,[26,29] older residents used less DAPs. Also consistent with other studies, higher number of drugs[29] and depression and Parkinson's disease[26,29] were positively associated with use of DAPs. However, in an Italian study cognitive impairment was associated with use of DAPs,[26] whereas in our study DAPs were prescribed mainly to residents with better cognition. Thus, older and more cognitively impaired residents appear to be more carefully assessed when prescribing drugs.

To our knowledge, very few studies have explored the relationships between increasing numbers of DAPs and users' characteristics. As in our study, in a small Norwegian study among nursing home residents a higher burden of DAPs according to the anticholinergic drug scale[30] was associated with younger age, milder cognitive impairment, and a higher number of drugs.[28]

There is also a paucity of studies investigating the association between DAP use and QOL.[12,13,26] Kolanowski and colleagues (2008)[13] examined use of DAPs and engagement in activities and found no association. Our previous study showed that DAP users had lower PWB than nonusers.[12] Landi et al. (2014)[26] found an association between use of DAPs and functional decline, which is a component of QOL. QOL is an important patient-related outcome, and thus, the negative and linear association between DAPs and PWB is a worrisome finding. Importantly, the same linear trend in PWB was seen both among those with and without depression and among those with and without functional dependence. These findings suggest that there is a true relationship between use of DAPs and poorer PWB.

In line with most earlier studies exploring the association between use of DAPs and mortality, we did not find a significant difference in mortality between DAP users and nonusers.[10]

Conclusions

In this study, the oldest residents with functional dependency and moderate cognitive decline were less often administered DAPs. Our study also suggests that the residents using DAPs had poorer PWB despite better cognition and functioning. Furthermore, there was a linear association between the number of DAPs and poor PWB irrespective of underlying depression or functional decline. Thus, clinicians should carefully consider the potential benefits and harms when prescribing these drugs to older people, even individuals with better cognition and functioning.

Acknowledgements: This study was suuported by the City of Helsinki and the Sohlberg Foundation. The funding sources had no role in the design or conduct of the study; in the collection, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

Legends to figures

Figure 1. Panel A: Psychological well-being (PWB) in groups using no drugs with anticholinergic properties (DAPs) (Group 0), using one DAP (Group 1), using two DAPs (Group 2), or using three or more DAPs (Group 3) among those having a diagnosis of depression (N=526) and those not having a diagnosis of depression (N=1895). In panel B PWB is presented in respective groups among those being dependent in ADL (Clinical Dementia Rating "Personal care": 3= needs help in dressing, personal hygiene, and taking care of personal belongings, 4= needs a lot of help in personal care, often incontinent) (N=1984) and those not dependent in ADL (N=448). Statistical significance for linearity across categories of anticholinergic properties groups were evaluated using generalized linear models with appropriate distribution and link function. Models included age and gender as covariates.

Table 1.

Characteristics of participants divided into groups using no drugs with anticholinergic properties (DAPs) (Group 0, G0), using one DAP (Group 1, G1), using two DAPs (Group 2, G2), or using three or more DAPs (Group 3, G3).

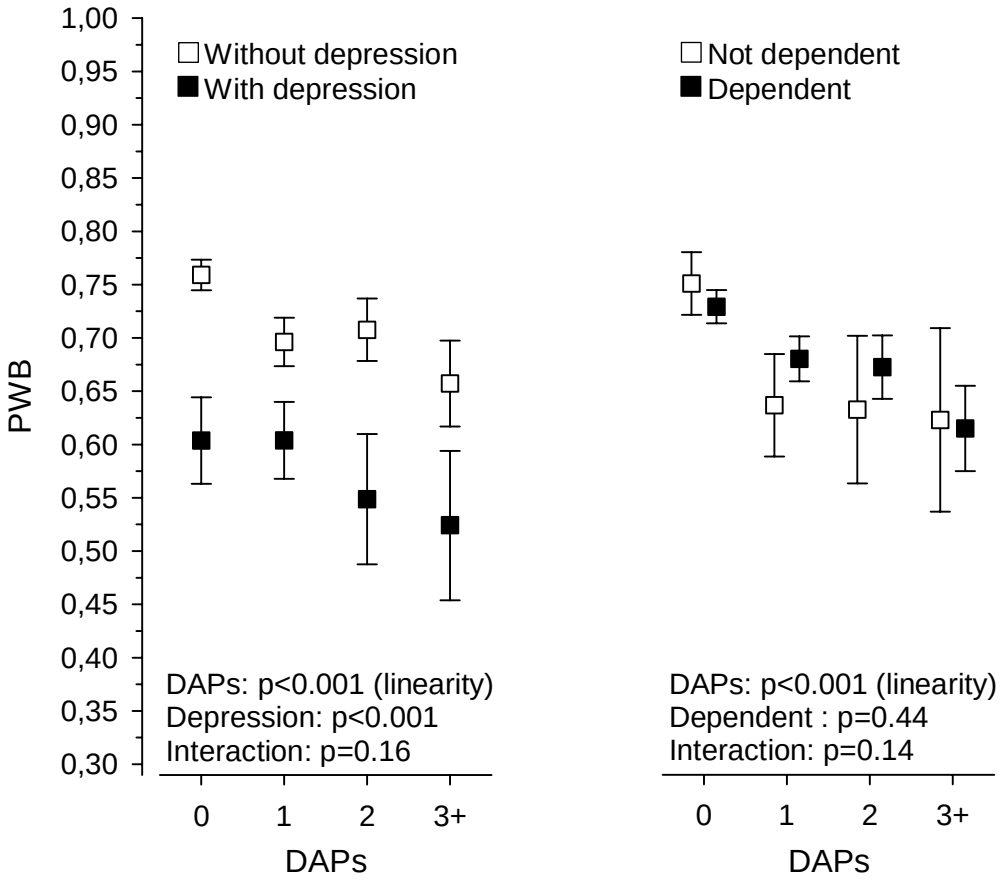
	Using no DAPs (G0) n=1191	Using one DAP (G1) n=682	Using two DAPs (G2) n=313	Using three or more DAPs (G3) n=246	p-value[1]
Females, n (%)	886 (74)	516 (76)	237 (76)	183 (74)	0.77
Age, mean (SD[2])	85 (7)	84 (8)	82 (8)	81 (7)	<0.001
Widowed, n (%)	682 (57)	342 (50)	129 (41)	83 (34)	<0.001
Education <8 years, n (%)	503 (42)	306 (45)	118 (38)	127 (52)	0.064
MNA[3], n (%)					0.96
<17, malnourished	238 (20)	119 (18)	49 (16)	45 (18)	
17-23, at risk for malnutrition	742 (63)	449 (66)	210 (68)	158 (64)	
>23, well-nourished	204 (17)	111 (16)	52 (17)	43 (17)	
Moderate cognitive decline (CDR 2)[4], n (%)	420 (35)	226 (33)	92 (29)	60 (24)	0.007
Dependent for personal care (CDR personal care class 2-3)[5], n (%)	960 (81)	566 (83)	256 (82)	202 (82)	0.066
Ability to walk inside, n (%)	599 (50)	386 (57)	175 (56)	132 (54)	0.25

1) p for trend, adjusted for age and gender
2) SD = standard deviation
3) MNA = Mini Nutritional Assessment (Vellas et al. 1999)[16]
4) CDR = Clinical Dementia Rating, "memory" item (Hughes et al. 1982)[17]
5) CDR "personal care" item (Hughes et al. 1982)[17]

Table 2. Participants' health, diseases, symptoms, and use of drugs according to groups using no drugs with anticholinergic properties (DAPs) (Group 0, G0), using one DAP (Group 1, G1), using two DAPs (Group 2, G2), or using three or more DAPs (Group 3, G3).

	G0 n=1191	G1 n= 682	G2 n=313	G3 n=246	p-value[1]
Self-rated health good, n (%)	790 (66)	442 (65)	214 (68)	131 (53)	0.016
CCI[2], mean (SD[3])	2.4 (1.5)	2.3 (1.5)	2.3 (1.6)	2.2 (1.5)	0.006
Dementia, n (%)	766 (64)	463 (68)	196 (63)	114 (46)	0.011
Depression, n (%)	194 (16)	172 (25)	84 (27)	76 (31)	<0.001
Other psychiatric diagnosis, n (%)	52 (4)	83 (12)	91 (29)	83 (34)	<0.001
Parkinson´s disease, n (%)	33 (3)	53 (8)	34 (11)	27 (11)	<0.001
COPD, n (%)	152 (13)	70 (10)	41 (13)	43 (17)	0.39
Gastric and duodenal ulcer, n (%)	23 (2)	14 (2)	3 (1)	12 (5)	0.42
Prior hip fracture, n (%)	178 (15)	86 (13)	37 (12)	30 (12)	0.32
Cancer, n (%)	107 (9)	61 (9)	30 (10)	20 (8)	0.99
Number of drugs used regularly, mean (SD[3])	7.1 (3.5)	8.8 (3.3)	9.5 (3.3)	10.1 (3.3)	<0.001
Number of *pro re nata* drugs, mean (SD[3])	3.0 (2.4)	3.3 (2.4)	3.3 (2.1)	4.1 (2.8)	<0.001
Dry mouth, n (%)	178 (15)	95 (14)	39 (12)	43 (17)	0.70
Constipation, n (%)	421 (35)	238 (35)	101 (32)	84 (34)	0.67
PWB[4], mean (SD[3])	0.73 (0.24)	0.67 (0.26)	0.67 (0.25)	0.62 (0.28)	<0.001
One-year mortality n (%)	238 (20)	134 (20)	56 (18)	50 (20)	0.11

1) p for trend, adjusted for age and gender
2) Charlson Comorbidity Index, CCI (Charlson et al. 1987)[18]
3) SD = standard deviation
4) Psychological Well-Being, PWB (Routasalo et al. 2009)[23]



Panel A Panel B

Figure 1.

References

1. Onder G, Liperoti R, Fialova D, et al. Polypharmacy in nursing home in Europe: results from the SHELTER study. J Gerontol A Biol Sci Med Sci 2012;67:698-704.

2. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. J Am Geriatr Soc 2015;63:2227-2246.

3. Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med 2008;168:508-513.

4. Dauphinot V, Mouchoux C, Veillard S, et al. Anticholinergic drugs and functional, cognitive impairment and behavioral disturbances in patients from a memory clinic with subjective cognitive decline or neurocognitive disorders. Alzheimers Res Ther 2017. https://doi.org/10.1186/s13195-017-0284-4.

5. Haasum Y, Fastbom J, and Johnell K. Institutionalization as a risk factor for inappropriate drug use in the elderly: A Swedish Nationwide Register-Based Study. Ann Pharmacother 2012;46:339-346.

6. Wawruch M, Macugova A, Kostkova L, et al. The use of medications with anticholinergic properties and risk factors for their use in hospitalized elderly patients. Pharmacoepidemiol Drug Saf 2012;21:170-176.

7. Palmer JB, Albrecht JS, Park Y, et al. Use of drugs with anticholinergic properties among nursing home residents with dementia: a national analysis of Medicare beneficiaries from 2007 to 2008. Drugs Aging 2015;32:79-86.

8. Gerretsen P, Pollock BG. Cognitive risks of anticholinergics in the elderly. Aging Health 2013;9:159-166.

9. Ruxton K, Woodman RJ, Mangoni AA. Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: A systematic review and meta-analysis. Br J Clin Pharmacol 2015;80:209-220.

10. Fox C, Smith T, Maidment I, et al. Effect of medications with anti-cholinergic properties on cognitive function, delirium, physical function and mortality: a systematic review. Age Ageing 2014;43:604-615.

11. Salahudeen MS, Duffull SB, Nishtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. BMC Geriatrics 2015 15:31. doi: 10.1186/s12877-015-0029-9.

12. Teramura-Grönblad M, Muurinen S, Soini H, et al. Use of anticholinergic drugs and cholinesterase inhibitors and their association with psychological well-being among frail older adults in residential care facilities. Ann Pharmacother 2011;45:596-602.

13. Kolanowski A**,** Fick DM, Campbell J, et al**.** A preliminary study of anticholinergic burden and relationship to a quality of life indicator, engagement in activities, in nursing home residents with dementia. J Am Med Dir Assoc 2009;10:252-257.

14. Suominen M, Muurinen S, Routasalo P, et al. Malnutrition and associated factors among aged residents in all nursing homes in Helsinki. Eur J Clin Nutr 2005;59:578-583.

15. Suominen MH, Sandelin E, Soini H, Pitkala KH. How well do nurses recognize malnutrition in elderly patients? Eur J Clin Nutr 2009;63:292–296.

16. Vellas B, Guigoz Y, Garry PJ et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition 1999;15(2):116-122.

17. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566-572.

18. Charlson ME, Pompei P, Ales K, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-383.

19. WHO Collaborating Centre for Drug Statistics Methodology. The Anatomical Therapeutic Chemical Classification System. WHO Collaborating Centre for Drug Statistics Methodology. Norwegian Institute of Public Health. https://www.whocc.no/atc_ddd_index/

20. Chapter 13 Cholinergic transmission. In: Rang HP, Ritter JM, Flower RJ, Henderson G. Rang and Dale´s Pharmacology. 8th ed. Elsevier, Churchill Livingstone, 2016.

21. Pitkala KH, Laakkonen ML, Strandberg TE, Tilvis RS. Positive life orientation as a predictor of 10-year outcome in an aged population. J Clin Epidemiol 2004;57:409-414.

22. Savikko N, Routasalo P, Tilvis R, et al. Loss of parents in childhood – associations with depression, loneliness and attitudes towards life in older Finnish people. Int J Older People Nurs 2006;1:17-24.

23. Routasalo PE, Tilvis RS, Kautiainen H, Pitkala KH. Effects of psychosocial group rehabilitation on social functioning, loneliness and well-being of lonely, older people: a randomized. controlled trial. J Adv Nurs 2009;65:297-305.

24. Huusko T, Kautiainen H, Pitkala K. WHOQOL-Bref and 150 in measuring quality-of-life among older caregivers. In: Huusko T, Strandberg T, Pitkala K. Can older people's quality of life be measured? [Finnish]. Helsinki, Finland: The Central Union for the Welfare of the Aged, 2006:76-90.

25. Kumpula EK, Bell JS, Soini H, Pitkälä KH. Anticholinergic drug use and mortality among residents of long-term care facilities: A Prospective Cohort Study. J Clin Pharmacol 2011;51:256-263.

26. Landi F, Dell´Aquila G, Collamati A, et al. Anticholinergic drug use and negative outcomes among the frail elderly population living in a nursing home. J Am Med Dir Assoc 2014;15:825-829.

27. Olsson J, Bergman A, Carlsten A, et al. Quality of drug prescribing in elderly people in nursing homes and special care units for dementia. Clin Drug Investig 2010;30:289-300.

28. Kersten H**,** Molden E, Willumsen T, et al. Higher anticholinergic drug scale (ADS) scores are associated with peripheral but not cognitive markers of cholinergic blockade. Cross sectional data from 21 Norwegian nursing homes. Br J Clin Pharmacol 2013;75:842-849.

29. Chatterjee S, Mehta S, Sherer JT, Aparasu RR. Prevalence and predictors of anticholinergic medication use in elderly nursing home residents with dementia: analysis of data from the 2004 National Nursing Home Survey. Drugs Aging 2010;27:987-997.

30. Carnahan RM, Lund BC, Perry PJ, et al. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. J Clin Pharmacol 2006;46:1481-1486.